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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,332	05/21/2001	Thomas G. Burke	434-204	5935

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/807,332	Burke
Examiner	**Art Unit**
Dave Nguyen	1632

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 3, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *9-25* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *9-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *5/21/01* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's species election without traverse of the adenovirus vector listed in claims 15 and 23 and the liposomes listed in claims 16 and 24 in the response filed October 3, 2002 is acknowledged.

Upon a search of prior art, the species restriction among viral vectors as claimed has been vacated by the examiner.

Claims 9-25 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 15, 18 and 24 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claims 10, 15, 18 and 24 embrace a viral vector such as an adenoviral vector, which contains within macromolecular assemblies a CPT/oligo complex. Applicant's contemplates on page 25, for example, that the CPTs complexes can be introduced, stored and delivered in a stable manner while being bound in the active lactone form to the oligos contained in the viral vectors. Applicant neither provides any guidance nor working examples so as to enable a skilled artisan to reasonably prepare such viral vectors within the framework of the claimed invention.

The state of the art of using viral vectors to deliver DNA (Verma, Nature, Vol. 389, 1997, 239-242) is that the DNA has to be prepared in an expressible structure, which comprises a regulatory sequence operably linked to a coding sequence of a desire DNA such as an antisense mRNA. However, the as-filed specification teaches that any oligonucleotide/CPT can be stored and maintained in a viral vector, and yet, the as-filed specification does not provide any guidance as to how CPT which is a toxic drug can be stored stably in any viral vector to the extent that the intended use of the viral vectors containing CPT/oligo complexes can be achieved so as to have a chemotherapeutic effect. The state of the art with respect to the use of CPTs in a virus (Pantazis, J. Biomedical Science, 6, 1, 1-7, 1999) is that CPT is a

potent inhibitor of replication, transcription and packaging of double-stranded DNA-containing adenoviruses, papovariruses and herpesviruses. As such, it is not apparent how a skilled artisan, without any undue experimentation, can prepare the claimed viral vectors so as to use within applicant's framework of the claimed invention, particularly in view of the reasons set forth above.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21 are rejected under 35 USC 102(a) as being anticipated by Thompson Strode, H. Peter Spielmann, and Andrew Wang, as co-authors of the reference cited in J. Am. Chem. Soc. 120, 2979-2980, Published on Web, March 12, 1998.

Thompson Strode, H. Peter Spielmann, and Andrew Wang (Strode) teaches that the hydrolysable alpha-hydroxy-lactone ring of any camptothecin used as a chemotherapeutic drug is essential for CPTs efficacy. In addition, Strode teaches that CTPs-duplex oligonucleotide complexes when prepared as a mixture of CPTs and synthetic oligonucleotides in a typical PBS buffer, promotes the complex formation between CPTs and the oligonucleotides and stabilizes the lactone forms of CPT (page 361 bridging page 362, and page 363).

Absent evidence to the contrary, the composition discloses in Strode has all of the functional properties as recited in the claims.

Claims 18-21 are rejected under 35 USC 102(b) as being anticipated by Chourpa (Specgtroscopy of Bviological Molecules: Modern Trends, [European Conferenceon Spectroscopy of Biological Molecules], 7th, Madrid, 1997.

Chourpa teaches it is well recognized in the prior art that the hydrolysable alpha-hydroxy-lactone ring of any camptothecin used as a chemotherapeutic drug is essential for CPTs efficacy. In addition, Chourpa teaches that CTPs-oligonucleotide complexes when prepared as a mixture of CPTs and synthetic oligonucleotides in a typical aqueous buffer at PH 7.3, promotes the complexation between CPTs and the oligonucleotides and stabilizes the lactone forms of CPT (page 361 bridging page 362, and page 363).

Absent evidence to the contrary, the composition discloses in Chourpa has all of the functional properties as recited in the claims.

Claims 9-13, 18-22, 24, 25 are rejected under 35 USC 103(a) as being unpatentable over Green *et al.* (US Pat No. 5,583,034) taken with either Strode or Chourpa (Specgtroscopy of Bviological Molecules: Modern Trends, [European Conferenceon Spectroscopy of Biological Molecules], 7th, Madrid, 1997, 361-362 alone, or further in view of Perez-Soler *et al.* (US Pat No. 5,834,012).

Green teaches a pharmaceutical composition for treating a tumor, wherein the pharmaceutical composition comprising a mixture of Camptothecins (CPTs) in a pharmaceutically acceptable buffer and/or carrier (column 8, lines 16-26, column 9, lines 11-24). Column 6, lines 36-66 of Green also discloses that liposomal carrier can be used to encapsulate and deliver the antisense oligonucleotide composition, and that any pharmaceutically acceptable buffer or aqueous solution can be used to prepare the antisense oligonucleotide composition. In addition, columns 11 and 12 disclose the sequence structure of the antisense oligos comprising GC base pairs. Green does not teach that lactone forms must be present in a Camptothecin, and that the antisense oligos are complexed in the pharmaceutical composition.

However, at the time the invention was made, it is well known in the prior art that (as evidenced by Chourpa and Strode), that the hydrolysable alpha-hydroxy-lactone ring of any camptothecin used as a chemotherapeutic drug is essential for CPTs efficacy. In addition, Chourpa and Strode both teach that CTPs-oligonucleotide complexes when prepared as a mixture of CPTs and synthetic oligonucleotides in a typical aqueous buffer promotes the complexation between CPTs and the oligonucleotides and stabilizes the lactone forms of CPT.

In addition, Perez-Soler *et al.* teaches that CPTs drugs are well described in the prior art and that liposomes can be used to trap and stabilize the lactone form of CPT (entire disclosure, particularly column 1 bridging column 2, and column 3).

It would have been obvious for one of ordinary skill in the art to have employed the pure lactone forms of CPTs as the chemotherapeutic drug in the pharmaceutical composition of Green. One would have been motivated to do so because is well-known in the prior art, as exemplified by Chourpa and Strode, that the hydrolysable alpha-hydroxy-lactone ring of any camptothecin used as a chemotherapeutic drug is essential for CPTs efficacy.

It would also have been obvious to one of ordinary skill in the art that the affinity between CPTs and antisense oligonucleotides so as to form a complex of CPTs and oligos is the intrinsic property of the CPTs when put in contact with oligonucleotides, particularly in light of the Chourpa reference which teaches as long as a mixture of CPTs and oligos is prepared in a typical buffer solution, complexes of CPTs and oligos are formed as a result of the affinity.

To the extent that the presently pending claims embrace the use of a liposomal carrier to protect and delivery an antisense oligo and CPT containing composition, it would have been obvious for one of ordinary skill in the art to have employed any known liposomal carrier to deliver the antisense oligo/CPT complexes present in the pharmaceutical composition of Green taken with Chourpa. One would have been motivated to do so because column 6, lines 36-66 of Green also discloses that liposomal carrier can be used to encapsulate and deliver the antisense oligonucleotide composition, and/or because Perez-Soler *et al.* teaches that CPTs drugs are well-described in the prior art and that liposomes can be used to stabilize the lactone form of CPT.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 10, 14, 18 and 22 are rejected under 35 USC 103(a) as being unpatentable over Green *et al.* (US Pat No. 5,583,034) taken with either Chourpa (Specgtroscopy of Bviological Molecules: Modern Trends, [European Conferenceon Spectroscopy of Biological Molecules], 7th, Madrid, 1997, 361-362 or Strode, and further in view of Matteucci (J. Am. Chem. Soc. 1997, Vol. 119, 6939-6940).

Green taken with either Chourpa or Strode is applied here as indicated above for the base claims 10 and 18. To the extent that Green taken with either Chourpa or Strode does not teach a covalent bonding between any oligonucleotide and the CPTs, Matteucci teaches that such conjugation has been prepared, that that the A and B rings of a CPT can be substituted in a variety of ways without the loss of activity, and further teach that triple helix forming oligos can be used to conjugate to CPTs so as to render sequence specific with respect to the activity of CPTs (page 6939).

It would have been obvious for one of ordinary skill in the art to have employed a covalent bond between CPTs and any oligo, including those disclosed in Green and/or Matteucci. One would have been motivated to do so because it is well-known in the prior art, as exemplified by Matteucci, to use a covalent bond to conjugate CPT to a oligonucleotide, and because Matteucci provides evidence showing that the A and B rings of a CPT can be substituted in a variety of ways without the loss of activity.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 18 and 22 are rejected under 35 USC 103(a) as being unpatentable over Chourpa (Specgtroscopy of Bviological Molecules: Modern Trends, [European Conferenceon Spectroscopy of Biological Molecules], 7th, Madrid, 1997, 361-362, and further in view of Matteucci (J. Am. Chem. Soc. 1997, Vol. 119, 6939-6940).

Chourpa is applied here as indicated above for the base claim 18. To the extent that Chourpa does not teach a covalent bonding between any oligonucleotide and the CPTs, Matteucci teaches that such conjugation has been prepared, that that the A and B rings of a CPT can be substituted in a variety of ways without the loss of activity, and further teach that triple helix forming oligos can be used to conjugate to CPTs so as to render sequence specific with respect to the activity of CPTs (page 6939).

It would have been obvious for one of ordinary skill in the art to have employed a covalent bond between CPTs and any oligo, including those disclosed in Chourpa and/or Matteucci. One would have been motivated to do so because it is well-known in the prior art, as exemplified by Matteucci, to use a covalent bond to conjugate CPT to a oligonucleotide, and because of the reasons set forth in Matteucci, particularly since Matteucci provides evidence showing that the A and B rings of a CPT can be substituted in a variety of ways without the loss of activity.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's response in the preliminary amendment (page 8 and 9) has been considered but is not found persuasive for the reasons set forth above. Applicant asserts that Green only teaches DMSO containing solutions of camptothecins. However, columns 6 and 9 of Green are not limited to applicant's response but rather embrace a pharmaceutical composition comprising a combination of CPTs and antisense oligonucleotides in any known pharmaceutically acceptable buffer including just a simple aqueous buffer. Applicant further asserts that the unique advantage as taught by the as-filed specification is not disclosed in Green, however, the fact that the unique advantage is not disclosed in Green alone does not render the claimed invention patentable, particularly since a complex of CPTs and oligos is the intrinsic property of the CPTs when put in contact with oligonucleotides, particularly in light of the Chourpa reference which teaches as long as a mixture of CPTs and oligos is prepared in a typical buffer solution, complexes of CPTs and oligos are formed as a result of the affinity.

No claim is allowed.

The drawings are objected in view of the reasons set forth in the attached PTO-948. A **complete response to this office action must include a response to the objection or a filing of corrected drawings so as to obviate the objection.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen

Primary Examiner

Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER